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Nonbullous pemphigoid: insights in clinical and diagnostic findings, treatment responses and prognosis

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ABSTRACT

Background: Nonbullous pemphigoid is an under-recognized phenotype of the autoimmune bullous disease pemphigoid, characterized by the absence of blisters. Several disease aspects have not been studied previously.

Objective: To describe the characteristics of nonbullous pemphigoid.

Methods: A retrospective chart review study. The diagnosis of pemphigoid was based on meeting two of the following three criteria; 1) pruritus, 2) positive direct immunofluorescence microscopy (DIF), 3) positive indirect immunofluorescence microscopy (IIF) on salt-split skin.

Results: Sixty-nine patients were included. The mean delay in diagnosis was 29 months. Skin examination most often showed pruritic papules/nodules (37%) or pruritus without primary skin lesions (22%). Histopathological findings were mainly nonspecific. DIF and IIF were positive in 60% and 69%. During follow-up blisters formed in 17%, which was associated with a positive IIF (p=0.014), and positive BP180 immunoblot result (p=0.032). The Kaplan-Meier estimates of 1-, 2- and 3-year mortality were 14%, 34%, and 46%, with an 8.6 fold increased all-cause mortality risk.

Limitations: The retrospective study design.

Conclusion: Nonbullous pemphigoid presented with heterogeneous pruritic skin lesions, resulting in delayed diagnosis. DIF and IIF are essential to diagnose nonbullous pemphigoid, in contrast to histopathology, mainly showing nonspecific findings. During follow-up, an increased all-cause mortality risk was observed.

CAPSULE SUMMARY

- Nonbullous pemphigoid is an under-recognized variant of pemphigoid with long diagnostic delays. Patients present with symptoms of pruritus, with or without skin lesions.
- Clinicians should realize that histopathology is not useful for diagnosing nonbullous pemphigoid; direct- and indirect immunofluorescence are required. Patients have an increased all-cause mortality risk.

LIST OF ABBREVIATIONS

BP	bullous pemphigoid
BMZ	basement membrane zone
CR	complete remission
DC	disease control
DIF	direct immunofluorescence microscopy
ELISA	enzyme linked immunosorbent assay
HR	hazard ratio
IIF	indirect immunofluorescence microscopy
MO	monkey oesophagus
NC16A	noncollagenous 16A domain of BP180
PR	partial remission
SMR	standardized mortality ratio
SSS	salt-split skin

INTRODUCTION

Pemphigoid is an autoantibody mediated skin disease mainly affecting elderly patients.[1] Autoantibodies target structural proteins BP180 and BP230 located in the basement membrane zone (BMZ), inducing an eosinophilic inflammatory response in the skin.[2] Interestingly, the immunological disease mechanism in pemphigoid can lead to two distinct clinical phenotypes, termed bullous and nonbullous pemphigoid.

Bullous pemphigoid (BP) classically presents with severe pruritus and tense blisters on urticarial plaques.[1] There is a high co-occurrence of psychiatric- and neurodegenerative diseases, and patients have an increased mortality risk compared to the age-matched general population.[3–6] One in five patients lack typical blisters, termed nonbullous pemphigoid.[7] Patients present with pruritus and a wide spectrum of skin manifestations that may resemble other pruritic skin diseases.[8–12] Consequently, patients often have a long diagnostic delay.[13,14] Urticarial plaques and papules/nodules are reported most frequently.[8–12] Blister development during disease course is reported in ten percent.[8]

The diagnosis of nonbullous pemphigoid is based on the detection of either skin-bound IgG or complement C3 in a linear deposition along the BMZ by direct immunofluorescence microscopy (DIF), and/or circulating antibodies by indirect immunofluorescence microscopy (IIIF) on salt-split skin (SSS).[7] Histopathology is often nonspecific.[8]

To date, little is known about the management and prognosis of nonbullous pemphigoid. Treatment recommendations of BP are often followed, recommending whole body application of superpotent topical corticosteroids as initial therapy.[15] The aim of this study was to describe the clinical and diagnostic findings, treatment responses, and follow-up of patients with nonbullous pemphigoid, to support early recognition and improve patient care.

MATERIALS AND METHODS

Selection of cases and data collection

This retrospective study included patients diagnosed with nonbullous pemphigoid between 2002-2017 at the dermatology department of the University Medical Center Groningen, the Netherlands. Inclusion criteria were based on recently established diagnostic criteria by Meijer et al. with two positive out of the following three criteria: 1) pruritus, 2) linear IgG and/or C3 depositions along the BMZ by DIF, 3) positive staining of IgG on the epidermal side of SSS substrate by IIF.[7] Exclusion criteria were blisters or vesicles prior to diagnosis, or at initial presentation objectified by a physician. Cases were excluded if blisters occurred within two months after the onset of pruritus, and considered prodromal BP.

Clinical characteristics were assessed by reviewing patient charts. Data was collected anonymously in electronic case report forms using Open Clinica software. The following variables were collected: age, date of first symptoms and diagnosis, clinical presentation, skin manifestations, diagnostic findings, treatment response, side effects, blister development and death during follow-up. The study was approved by the Institutional Review Board at our local ethics committee.

Laboratory tests for pemphigoid

Laboratory techniques DIF, IIF on SSS and monkey oesophagus (MO), and immunoblot were performed at our Immuno-dermatology Laboratory as reported previously.[7] Autoantibodies against the noncollagenous 16A domain of BP180 (NC16A) and BP230 were detected with commercially available enzyme linked immunosorbent assays (ELISA) according to the manufacturer's protocol (MBL Japan, cut-off index ≥ 9 u/mL).

Treatment response and safety

Treatment response was assessed by using outcome measurements defined by international consensus, consisting of disease control (DC), partial remission (PR) on minimal/off therapy, complete remission (CR) on minimal/off therapy, and relapse.[16] We deviated from the consensus definition by allowing a dose of 7.5 mg methotrexate per week to count for minimal therapy. Reported side effects were registered. Uncertainties during retrospective assessment were resolved through discussion with the study team.

Statistical analysis

Correlations between bivariate outcomes were analyzed with the Pearson Chi-Square test, or Fisher's exact test when appropriate. Comparisons of means for non-normally distributed data were done with the Mann-Whitney U test. Estimated cumulative survival after 1-, 2-, and 3-year follow-up was assessed by Kaplan-Meier analysis. Univariate cox regression was performed to investigate the effect of selected variables on the 3-year survival. Age-adjusted standardized mortality ratios (SMR) were calculated by comparing the objectified 1-year all-cause mortality rates in nonbullous pemphigoid with the expected 1-year all-cause mortality rates per age group, using mortality data of the Dutch population over the year 2017, provided by Statistics Netherlands (CBS, www.cbs.nl). The 95% confidence interval for SMR was calculated using Poisson distribution.[17] A p-value <0.05 was defined as statistical significance. Statistical analyses were performed using IBM SPSS statistics version 23.

RESULTS

Patient characteristics and clinical findings

Patients' characteristics are shown in table 1. Patients were relatively old (mean 76.1 years), and had several comorbidities, such as hypertension (34%), diabetes mellitus (24%), atrial fibrillation (13%), and stroke (12%). ACE inhibitors and loop diuretics were used in 26% and 20%. Six individual patients reported a time relation with onset of symptoms and the use of acenocoumarol, simvastatin, candesartan, metoprolol, perindopril and acitretin.

Observed skin lesions are displayed in figure 1. Fifteen patients (22%) presented with pruritus on primary, nondiseased, noninflamed skin, and showed a significantly longer delay in diagnosis compared to patients with primary skin lesions (49.9 vs. 22.6 months; p=0.018).

The average duration of follow-up was 22 months, but varied per patient (0-218 months). Factors influencing the follow-up duration include death during follow-up, response to therapy, and transfer of care of elderly patients with physical limitations or long travel distance. Follow-up was longer in patients with systemic treatment.

Diagnostic findings

Diagnostic findings are summarized in table 2. Histopathology most often showed a dermal perivascular infiltrate (98%) with eosinophils (69%), and a subepidermal split in only one case. Pathologists most frequently reported nonspecific findings (n=21; 39%), or findings compatible with cutaneous drug reactions (n=18; 33%), eczema (n=12; 22%), urticaria (n=6; 11%), chronic scratching (n=5; 9%), insect bites (n=3; 6%), or a psoriasiform dermatitis (n=3; 6%).

DIF results were positive in 41 of 69 cases (60%), of which 20 cases (29%) had a positive IIF on SSS result, and 21 cases (31%) a negative result. In ten of these 21 cases circulating antibodies against BP180 or BP230 were demonstrated by immunoblot or ELISA.

In 27 of 69 cases (40%) DIF was negative and the diagnosis based on a positive IIF on SSS and compatible pruritic symptoms. Additional positive results by IIF on MO, ELISA and immunoblot were found in 26 (96%), 21 (78%) and 17 (63%) cases. In one case DIF was not performed, and the diagnosis based on IIF on SSS positivity.

Immunoblot and ELISA showed that autoantibodies were predominantly directed against BP230. BP230 reactivity correlated with negative DIF (p=0.019).

Conversely, BP180 reactivity correlated with positive DIF (p=0.048). In cases with only BP230 reactivity and no BP180 autoantibodies, a stronger association was seen (p=0.001). In 16 cases ELISA titers of IgG against NC16A and BP230 were repeated during follow-up, and changes corresponded to clinical symptoms in seven, and did not corresponded in nine cases.

Treatment response

Treatment strategy could vary for individual patients, due to ineffectiveness of prescribed topical or systemic therapies prior to diagnosis, or individual patient characteristics and comorbidities. Treatment response to initial and second prescribed therapies are displayed in table 3. Topical corticosteroids were often prescribed awaiting diagnostic test results. Twenty-two patients reported side effects during the complete follow-up period. Side effects were experienced by 47% of the patients treated with methotrexate (n=32), and treatment needed to be discontinued in 28%. Azathioprine (n=10) and dapsone (n=6) gave side effects in 50% of the cases.

Disease course

Twelve of 69 cases (17%) developed blisters during follow-up, after a mean disease duration of 41.4 months (SD 65.9; R 5-242). Four patients were in remission off therapy at the time blisters formed, and six patients in remission on minimal systemic therapy. Two patients developed blisters during initially prescribed whole body application of superpotent topical corticosteroids. The mean follow-up time of cases with blister formation was significantly longer (41.4 months (SD 58.2; R 2-218)) compared to patients without blister formation (17.7 months (SD 31.7; R 0-172; p=0.008)).

Blister development during follow-up was associated with positive IIF on MO/SSS (p=0.014), and positive BP180 immunoblot (p=0.032). Immunoserology tests and DIF were repeated in three of 12 cases with blister formation. Increased autoantibody titers against both NC16A and BP230 were detected by ELISA in two of three cases. DIF was already positive at diagnosis in two cases; in the third case DIF turned out positive after blisters occurred. Nevertheless, the alteration from negative to positive DIF during follow-up was also observed in four cases without blister development.

Mortality rates

Twenty-five patients (36%) died during follow-up, after mean disease duration of 51.2 months (SD40.6; R16-153). The mean time between diagnosis and death was 24.1 months (SD26.3; R0-127). Causes of death were lung cancer (n=1), sepsis after a surgical procedure (n=2), heart failure (n=2), and most often unknown (n=20). Ten patients were lost to follow-up within the 1-year follow-up period, and four additional patients within the 3-year follow-up period, mainly due to referral to a peripheral hospital after the diagnosis was made. The Kaplan-Meier estimates of 1-, 2-, and 3-year all-cause mortality in nonbullous pemphigoid were 14%, 34%, and 46%. Univariate Cox Regression analysis showed a significant effect of age on the 3-year survival (HR 1.04; p=0.028). No other factors significantly influenced the 3-year mortality risk in our population. The SMR per age group is displayed in table 4, showing an 8.6-fold increased all-cause mortality risk in the overall nonbullous pemphigoid population.

DISCUSSION

Patients with nonbullous pemphigoid endured symptoms for an average duration of 29 months before the correct diagnosis was made. Our study confirmed that histopathological findings in nonbullous pemphigoid are nonspecific, and DIF and IIF should be performed to establish the diagnosis of nonbullous pemphigoid. Methotrexate was most successful in achieving remission, though side effects were reported by almost half of the patients. Of importance, an increased all-cause mortality risk was demonstrated, indicating that a lack of blisters is not equivalent to a mild prognosis.

We found a considerable longer diagnostic delay in nonbullous pemphigoid, compared to BP (29 vs. 6 months).[18] Dermatologists should perform DIF and IIF on SSS even in the absence of blisters when considering pemphigoid. The low-hanging fruit of unrecognized nonbullous pemphigoid can easily be harvested by the aforementioned tests in elderly patients with refractory chronic pruritus. The diagnostic value of routine histopathology for the diagnosis of pemphigoid is poor. Eosinophilic spongiosis and a subepidermal split are considered histopathological hallmarks of BP.[1] In fact, these findings are less typical than implied, as a recent study could only confirm eosinophilic spongiosis in 50% and a subepidermal split in 54% of BP cases.[19] We observed that only in 6% of the nonbullous pemphigoid cases eosinophils infiltrated the epidermis. Furthermore, eosinophils were found in a perivascular infiltrate (69%), and in the peripheral blood (45%). Eosinophils are hypothesized to mediate blister formation through secretion of toxic granule proteins.[20,21] In nonbullous pemphigoid eosinophils may be activated and attracted towards the skin, but may be unable to infiltrate the epidermis and induce blistering.

A notable observation is the predominant reactivity against BP230 in nonbullous pemphigoid, correlating with a negative DIF result, also described by previous studies.[8,22,23] It is suggested that the intracellular localization of BP230 might hinder binding of autoantibodies in skin, resulting in negative staining by DIF.[24] In contradiction, we found ten nonbullous pemphigoid cases with positive DIF, and only circulating BP230 autoantibodies. Meijer et al. previously showed that autoantibodies against BP180 NC16A are more often present in BP compared to nonbullous pemphigoid, and serum titers appear higher.[7] The pathogenicity of BP180 autoantibodies was repeatedly confirmed *in vitro* and *in vivo.*[7,25] In contrast, BP230 autoantibodies failed to spontaneously induce blisters in several animal studies.[25,26] Several studies suggest that symptoms and binding capacity of BP230 autoantibodies depend on coinciding intracellular epitope exposure, for instance by

ultraviolet irradiation, epithelial injury, or the transient presence of BP180 autoantibodies.[27,28] Recently, BP230 autoantibodies were found to bind in the skin and induce blisters in scurfy mice lacking regulatory T cells.[29] Based on these findings we suggest that loss of regulatory T cell function, seen in the aging process, might also influence the pathogenic ability of circulating BP230 antibodies. Other studies linked epitope recognition to BP phenotype, with less inflammation when antibodies recognized the middomain of BP180, or the C-terminal domain of BP230 in cases with BP230 antibodies only.[24,30] Future studies are needed to illuminate the pathophysiology of nonbullous pemphigoid.

Interestingly, five patients with initial negative DIF results turned positive when DIF was repeated. This demonstrates that the used minimal diagnostic criteria truly support early diagnosis in pemphigoid.[7] The changed DIF result coincided with blister development in one case, and in general no trend of altered antigen recognition, or relation with biopsy site was observed in these patients.

Our study provides data concerning treatment responses in nonbullous pemphigoid, with only limited data available on the treatment of localized cases. In generalized cases, the highest effectiveness was seen of methotrexate, followed by lesional clobetasol cream and whole body application of superpotent topical corticosteroids. Caution is advised for treatment with methotrexate in elderly patients, as many side effects were reported. Prednisolone often led to DC (58%), though all patients relapsed over time, suggesting it is useful for short-term disease control only. Lesional corticosteroids were ineffective in most cases, however, remission was still seen in 28%. Williams et al. showed non-inferiority of a treatment strategy starting doxycycline over prednisolone in BP.[31,32] Our data showed that doxycycline was not effective in the majority (86%) of nonbullous pemphigoid patients.

Prognostic data of our study showed that 36% of the study population died after an average disease duration of 51.2 months. Compared to BP we found a lower 1-year all-cause mortality rate in nonbullous pemphigoid, and similar to higher 2- and 3-year all-cause mortality rates.[5,6,33] Moreover, an overall SMR of 8.6 was found in nonbullous pemphigoid compared to reported SMR of 3.4, 3.6 and 6.6 in BP.[5,6,33] Our mortality data might be influenced by the low sample size, and limited follow-up data of cases that were censored in the Kaplan-Meier analysis. Furthermore, it can be hypothesized that the long delay in diagnosis, and therefore prolonged disease exposure without adequate treatment, might influence the prognosis.

A limitation of this study was the retrospective design. Consequently, disease severity measurements such as the BPDAI and autoantibody titers during follow-up

were not available. Moreover, the cause of death was unknown to the authors in 20 of 25 deceased cases. A selection bias might affected epidemiology, treatment and prognostic results, since patients visiting an academic hospital are more likely to have severe complaints. Furthermore, our cohort misses patients residing in nursing homes who are not be able to visit a hospital, which could explaining the low co-occurrence of neurodegenerative diseases in our cohort.[3,4] Another limitation was the significant shorter follow-up in cases without blister formation, not allowing us to draw hard conclusions on the number of patients with late blister development.

This study brought insight in unrevealed disease aspects of nonbullous pemphigoid. Most important, pathologists and dermatologists should be aware that nonbullous pemphigoid cannot be excluded by histopathology and performance of DIF and IIF are required for diagnosis. Once the diagnosis is established, the best therapeutic effect was seen with methotrexate. The mortality rates in nonbullous pemphigoid are increased, indicating that a lack of blisters is not equivalent to having a better prognosis.

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TABLES

Table 1

Table 1. Clinical characteristics of patients with nonbullous pemphigoid

General characteristics	**Mean (SD; Range) or n (%)**
Mean age at diagnosis, years	76.1 (13.5; 39-101)
Gender, n / n	29 M / 40 F
Mean delay in diagnosis, months	28.9 (53.7; 0-385)
Mean time of follow-up, months	21.9 (38.2; 0-218)
Living in a nursing home, n (%)	7 (11.5)
Location of symptoms	**n (%)***
Extremities	58 (92.1)
Back	46 (79.3)
Abdomen	29 (55.8)
Scalp	18 (34.0)
Hands/feet	16 (32.0)
Neck	17 (31.5)
Face	6 (12.0)
Mucosa	0 (0.0)
Findings during skin examination	**n (%)***
Pruritus**	68 (98.5)
generalized pruritus	40 (58.0)
excoriations	52 (76.5)
Localized disease**	6 (8.7)
Xerosis cutis	8 (11.8)
Papules/nodules	21 (30.9)
Pruritus on primary nondiseased, noninflamed skin	15 (22.1)
3 sensu stricto	
Urticarial papules/plaques	8 (11.8)
1 with pustules	
Eczematous lesions	3 (4.4)
Mixed skin findings	
Urticarial papules/plaques + papules/nodules	10 (14.7)
Papules/nodules + eczematous lesions	1 (1.5)
Papules/nodules + erythematous macules	3 (4.4)
Other	7 (10.3)
4 Erythematous plaques with squamous borders	
2 pityriasis rubra pilaris-like	
1 Suberythrodermia	
1 Ulcerations	
1 Localized livid, erythematous macules	

*M, male; F, female; SD, standard deviation; R, range; ACE, angiotensin converting enzyme; DPP4, dipeptyl peptidase-4; * percentages were calculated after exclusion of cases of which data was unknown. ** Data extracted from anamnesis. ***Localized disease was defined as the presence of localized lesions involving one body site, conform the European consensus on the management of bullous pemphigoid 2015.*[15]

Table 2

Table 2. Diagnostic findings in nonbullous pemphigoid

Histopathology (n=54)	**n (%)***
Subepidermal split	1 (1.9)
Spongiosis	22 (40.7)
without inflammatory cells	12 (22.2)
Eosinophilic spongiosis	3 (5.6)
Lymphocytic spongiosis	7 (13.0)
Dermal lymphocytic infiltrate	53 (98.1)
located perivascular	49 (90.7)
presence of eosinophils	37 (68.5)
DIF on a skin biopsy (n=68)	**n (%)***
Positive DIF result	41 (60.3)
IgG	41 (60.3)
C3c	14 (20.6)
IgA	10 (14.7)
IgM	5 (7.4)
n-serrated pattern	19 of 41 (46.3)
indeterminable serration pattern	22 of 41 (53.7)
Immunoserological findings (n=68)	**n (%)***
Positive IIF result	47 (69.1)
IIF on MO, IgG	42 (61.8)
IIF on SSS, IgG	45 (66.2)
IIF on SSS, IgA	5 (7.4)
Positive immunoblot results	37 (54.4)
BP180	9 (13.2)
BP230	28 (41.2)
BP230 doubtful	5 (7.4)
Positive ELISA results	41 (60.3)
NC16A, n (%); mean titer u/mL	21 (30.9); 44.6 (SD 31.4; R 11-146)
BP230, n (%); mean titer u/mL	30 (46.9); 39.7 (SD 29.5; R 11-122)
Eosinophilia in peripheral blood (n=57)	26 (44.8)
Mean titer, 10E9/L	1.02 (SD 0.61; R 0.4-2.4)

DIF, direct immunofluorescence microscopy; IIF, indirect immunofluorescence microscopy; MO, monkey oesophagus; SSS, salt split skin; LAD-1, linear IgA disease-1; ELISA, enzyme linked immunosorbent assay; NC16A, noncollagenous 16a; SD, standard deviation; R, range.

** Percentages were calculated after exclusion of cases of which data was unknown.*

Table 3

Table 3. Treatment response on first and second prescribed therapies in localized and generalized nonbullous pemphigoid.*

		Response unknown	No response	DC	time till DC, weeks	Remission, either PR/CR	PR	time till PR, weeks	CR	time till CR, weeks	relapses	time till relapse, weeks
Localized[a] nonbullous pemphigoid (n=6) First (n=6) and second (n=2) therapies	**n**	**n**	**n (%)****	**n (%)****	**mean (SD; R)**	**n (%)****	**n (%)****	**mean (SD; R)**	**n (%)****	**mean (SD; R)**	**n (%)*****	**mean (SD; R)**
Lesional clobetasol cream	2	-	2 (100.0)	-	-	-	-	-	-	-	-	-
Doxycyline	2	-	1 (50.0)	-	-	-	-	-	1 off (50.0)	5.0	-	-
whole body application of superpotent topical corticosteroids	1	1	-	-	-	-	-	-	-	-	-	-
Triamcinolon lesional	1	-	-	-	-	-	-	-	1 on (100.0)	5.0	-	-
Methotrexate[b]	1	-	-	1 (100.0)	11.0	-	-	-	-	-	-	-
Azathioprine[c]	1	-	1 (100.0)	-	-	-	-	-	-	-	-	-
Generalized nonbullous pemphigoid (n=61) First (n=61) and second (n=42) therapies	**n**	**n**	**n (%)****	**n (%)****	**mean (SD; R)**	**n (%)****	**n (%)****	**mean (SD; R)**	**n (%)****	**mean (SD; R)**	**n (%)*****	**mean (SD; R)**
Whole body application of superpotent topical corticosteroids	41	2	11 (28.2)	18 (46.2)	7.4 (8.3; 2-37)	10 (25.6)	4 on (10.3); 1 off (2.6)	17.8 (6.9; 9-28)	1 on (2.6); 4 off (10.3)	17.0 (11.1; 5-31)	12 (42.9)	41.8 (80.3- 2-275)
Methotrexate (+ short-term prednisolone in 3)	15	1	3 (21.4)	5 (35.7)	11.8 (11.4; 3-29)	6 (42.9)	4 on (28.6); 1 off (7.1)	38.8 (31.5; 8-87)	1 on (7.1)	19.0	5 (45.5)	94.6 (100.0; 8-254)
Prednisolone	13	1	3 (25.0)	7 (58.3)	4.3 (6.2; 1-18)	2 (16.7)	1 on (8.3)	17.0	1 on (8.3)	12.0	9 (100.0)	9.9 (5.3; 1-20)
Lesional clobetasol cream	10	1	4 (44.4)	1 (11.1)	7.0	4 (44.4)	2 on (22.2); 1 off (11.1)	8.7 (8.0; 1-17)	1 off (11.1)	20.0	1 (20.0)	9.0
Doxycyline (with or without nicotinamide)	5	-	5 (100.0)	-	-	-	-	-	-	-	-	-
Prednisolone + doxycycline	3	-	1 (33.3)	2 (66.7)	1.0 (0.0; 1-1)	-	-	-	-	-	1 (50.0)	5.0
Whole body application of superpotent topical corticosteroids + doxycycline	2	-	1 (50.0)	1 (50.0)	4.0	-	-	-	-	-	1 (100.0)	3.0
Prednisolone + azathioprine	3	-	1 (33.3)	2 (66.7)	3.0 (1.7; 2-5)	-	-	-	-	-	1 (50.0)	14.0
Dapson	3	1	1 (50.0)	1 (50.0)	8.0	-	-	-	-	-	1 (100.0)	1.0
Other therapies 3 Mometason (lesional, + tacrolimus in 2) 3 Triamcinolon (lesional) 1 Terbinafine (systemic) 1 Tacrolimus (lesional, topical)	8	-	4 (50.0)	3 (37.5)	3.0 (1.7; 2-5)	1 (12.5)	1 off (12.5)	2.0	-	-	-	-

DC, disease control; PR, partial remission; CR, complete remission; on/off, on minimal/off therapy, as defined by international consensus[1]; SD, standard deviation; R, range.

** Two cases did not receive therapy, one patient had minimal complaints and was lost to follow-up, and one first stopped suspected related medication and died shortly after.*

*** Percentages were calculated without taking unknown responses into account. *** Percentages of patients relapsing were calculated over the number of cases that achieved DC, PR or CR.*

[a] Localized disease was defined as the presence of localized lesions involving one body site, conform the European consensus on the management of bullous pemphigoid 2015.[15]

[b] This patient had psoriasis, methotrexate was chosen as treatment for both skin diseases. [c] This patient used low dose azathioprine for Crohn's disease, the dose was heightened when pemphigoid was diagnosed.

Table 4

Table 4. Standardized mortality ratio's (SMR) in nonbullous pemphigoid

Age groups	Total, n	Mortality, n	Expected 1-year mortality*	Observed 1-year mortality	SMR	95% CI
30-59	7	0	0.0018	0.0000	0.0	0.0 - 2.1
60-69	10	1	0.0089	0.1000	11.2	9.1 - 13.7
70-79	19	2	0.0243	0.1053	4.3	3.5 - 5.2
80-89	26	5	0.0806	0.1923	2.4	2.1 - 2.7
90 or older	7	0	0.2643	0.0000	0.0	0.0 - 0.1
Total group (aged ≥30)	69	8	0.0134	0.1159	8.6	7.1 - 10.3

*SMR, standardized mortality ratio; CI, confidence interval. * Expected deaths in the Dutch population are based on population wide data of the year 2017.*

FIGURE 1

Figure 1. Nonbullous pemphigoid presenting with pruritus and various skin lesions. A. Papules and nodules. B. Pruritus on primary nondiseased, noninflamed skin with secondary excoriations. C. Urticarial papules and plaques. D. Eczematous lesions.